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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,949	02/03/2004	Paul A. DiTullio	21578-002 CON	3766

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/771,949	DITULLIO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8,11-14,17,18 and 21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 8, 11-14, 17, 18, and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/247,246, now US Patent 6,686,199.

Claims 1, 2, 5, 6, 8, 11-14, 17, 18, and 21-26 remain pending and are under consideration in this Office Action.

Priority

The specification has been amended to indicate the allowance of the priority application, however the amendment deleted the required statement of the relationship between the priority document and this application. For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. See MPEP 201.11 (III)(A).

Claim Objections

Applicant's amendments overcame the previous objections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 8, 11-14, 17, 18, and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 2, 5, 6, 8, 11-14, 17, and 21-25 are directed to methods of delivering a DNA to a spermatogonium of a chicken. The only purpose for the method disclosed in the specification is to make transgenic chickens, so enablement of the claims will be assessed accordingly.

The specification teaches that transgenic animals in general are used for xenotransplantation, pharmaceutical production, protein production, and the study of human diseases. The specification taught no specific use for transgenic chickens. The prior art indicated interest in the use of transgenic chickens as bioreactors for protein production. The prior art of record did not envision the use of chickens for xenotransplantation or the study of human diseases.

Afanassieff et al (Avian Dis. 40 :841-852, 1996) taught intratesticular inoculation of avian leukosis retrovirus into adult and 1-week old brown leghorn chickens to investigate the possibility of producing transgenic chickens. However, no evidence of viral nucleic acid was detected after 6 weeks in prepubertal birds, and no viral nucleic acid was present in the semen of the adult birds (see page 845, column 2, first full paragraph, and paragraph bridging columns 1 and 2 on page 846). The data are consistent with elimination of virally-infected cells by the host immune system. See abstract, and first full paragraph of column 2 on page 849.

Li et al (Transg. Res. 4 :26-29, 1995) taught delivery of transgenes to primordial germ cells of the germinal crescent by gene gun. Chimeric hatchlings raised to maturity contained transgenes in their sperm. These birds were mated to produce G1 offspring. Twenty percent of the G1 offspring retained the transgene, but in the majority of cases, the DNA disappeared by maturity. See abstract. Li did not assess gene expression.

Ebara et al (Asian J. Androl. 1(3) : 139-144, 1999) taught transfection with microinjected naked DNA of germinal crescent cells in male and female chickens to produce chimeric birds. DNA was subsequently detected in the sperm cells of male chimeric chickens (see page 141, column 2, second and third full paragraphs and Table 4). Chimeric birds were bred, and transgene inheritance and expression in offspring was assessed. In no case did expression persist past the late embryo stage, and the introduced DNA was no longer detectable after 4 months in any bird. See item 3.2, Fig. 2, and Table 2 on page 141; paragraph bridging pages 142 and 143.

Sugihara et al (Comp. Biochem. Phys. B 125:47-52, 2000) taught foreign gene expression in quail testes by in vivo electroporation. Vectors used included episomally replicating vectors, and non-replicative vectors that would require chromosomal integration for stable transfection (see Fig. 1 on page 49). Regardless of the type of plasmid used, gene expression in testis was transient, even though a variety of constitutive promoters was used (CMV promoter, SV40 promoter/enhancer, RSV LTR, and beta actin promoter/enhancer, see Fig. 1).

In summary, at the time the invention was filed, no bird expressing a transgene had been produced by methods in which nucleic acids were delivered to progenitors of

sperm cells, regardless of the age of the bird at the time the transgene was introduced. As a result the field of making transgenic birds by genetic modification of spermatogonia is considered to be immature, and highly unpredictable.

The instant specification provides no working example. Guidance in the specification as to how to improve on the results in the prior art is limited to the suggestion of the use of selectable markers and corresponding drugs to select for spermatogonial cells comprising the transgene. However, there is no precedent in the prior art of record for such in vivo selection of spermatogonial cells. Also, it is clear that such selection would, if it were feasible, only select for the presence of the transgene, and not necessarily for transgene integration. As seen in the art discussed above, non-viral transgenes that were present in spermatogonia did not become stably integrated into the genome, were not expressed in transgenic hatchlings, and were subsequently lost.

In view of the immature state of the art as discussed above, the high level of unpredictability, and absence of any working example in the specification, and the lack of adequate guidance, one of skill in the art could not practice the invention as intended (i.e. for the production of transgenic chickens) without undue experimentation.

Claim 18 is directed to a method of making a transgenic chicken by delivering a DNA to a testicle of a chicken, harvesting sperm cells from the chicken, and contacting an ovum with said sperm cells under conditions suitable for fertilization. It lacks enablement for the same reasons discussed above. In addition, note that there is no nexus between the nucleic acid infused into the testicle and the sperm cells isolated

from the chicken. While the specification teaches that DNA is infused into the testicle to transfect spermatogonial cells, which ultimately leads to the production of transgenic sperm, claim 18 does not require transfection of spermatogonial cells or any other cells including sperm. Regarding the embodiment in which no cell is transfected, the specification provides no guidance as to how to avoid degradation of the DNA in seminal fluid.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a DNA to a spermatogonium, comprising infusing in situ said DNA into a testicle of a prepubertal non-human mammal and administering a lipid or phospholipid to said testicle to facilitate uptake of said DNA by said spermatogonium, wherein said DNA is infused into said testicle before production of sperm by meiosis in said testicle, does not reasonably provide enablement for the broader method of delivering a DNA to a spermatogonium of animals other than mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 26 is drawn to a method of delivering a DNA to a spermatogonium of any animal. The only purpose for the method disclosed in the specification is to make transgenic animals, so enablement of the claims will be assessed accordingly. The only non-mammalian transgenic animal contemplated by the specification is a chicken. This scope of the invention is not enabled for the reasons set forth above. Regarding the

broader scope of non-chicken animals, the specification is considered enabling for non-human mammals, as indicated in the US Patent 6,686,199. The broader scope of non-human, non-mammalian, non-chicken animals is not enabled due to the state and unpredictability in the art as discussed above, the lack of any working example in the specification, and the lack of any guidance specific to other animals such as reptiles, non-chicken birds, or insects. One of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments, and the Declaration of Paul A. DiTullio, filed 10/5/06 have been full considered but are unpersuasive.

Applicant argues that the claimed methods were used to incorporate a transgene into the spermatogonia of a rooster and the treated spermatogonium produced transgenic sperm. Applicant relies for support on the Declaration of Paul A. DiTullio. The Declaration summarizes an experiment in which a lipid/DNA complex was injected into the testes of white leghorn roosters. The age of the roosters is not disclosed. The roosters were either allowed to reach sexual maturity in order to collect semen for transgene analysis, or were sacrificed after 1 week to assess transgene delivery. Genomic DNA for PCR was isolated from semen or testes. Fluorescent in situ hybridization (FISH) was performed on semen from a single bird using a transgene probe. Declarant indicates that a positive result was obtained. A second bird produced

semen that were positive by PCR. However, the data presented are not indicative of integration into genomic DNA. PCR is extremely sensitive and could detect contaminating plasmid DNA in the samples. It is also unclear as to whether or not the FISH assay detected chromosomal integration or contaminating plasmid DNA. As discussed above in the rejection, the art of making transgenic birds by injection of DNA is highly unpredictable. Even in cases where DNA is transmitted to offspring, it is generally not expressed and is lost from the birds. See Afanassieff, Li, and Ebara above. These studies are consistent with the loss of non-integrated DNA. The Declaration of DiTullio provides no persuasive evidence of DNA integration into the bird genome, so it is not clear that the method overcomes this problem. Further, the teachings of Sugihara show that gene expression in the testes of transgenic birds is very unpredictable. For these reasons the rejections are maintained.

Double Patenting

The double patenting rejection is withdrawn in view of the submission and approval of a terminal disclaimer over US 6,686,199.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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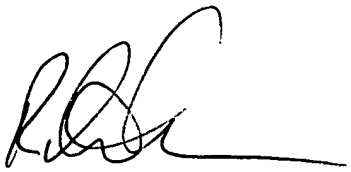

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Art Unit 1635